



#### REMARKS

Claims 284-336 are pending in this application. New claims 337-372 have been added. No claims have been amended or canceled. Accordingly, claims 284-372 are being presented for further examination on the merits.

A minor amendment to the specification (page 2) has been effected above. A copy of U.S. Patent No. 5,476,928 (issued on December 19, 1995) referenced in the above amendment to the specification is attached as Exhibit 1.

The addition of new claims 337-372 above follows Applicants' March 28, 1997 Amendment Under 37 C.F.R. §1.115. Entry of the new claims is respectfully requested.

New claims 337-372 are directed to two embodiments of the present invention. In the first embodiment as exemplified in new independent claim 337, there is recited a process of preparing a labeled oligo- or polynucleotide of interest. The two-step process includes a first step of providing the chemically modified nucleotides of the invention at hand and a second step of incorporating them with other modified or unmodified nucleic acids in the oligo- or polynucleotide of interest, thereby preparing a labeled oligo- or polynucleotide of interest. The other dependent claims being added are directed to the linkage group (claims 338-341); enzymatic incorporation (claims 342-344); the use of nucleoside di- or tri-phosphates as chemically modified nucleotides or other modified or unmodified nucleic acids (claim 345); and template dependent or template independent incorporation (claims 346-347).

In the newly claimed second embodiment as set forth in claims 348-372, the present invention is directed to a process for detecting the presence of an oligo- or polynucleotide of interest in a sequencing gel. The main independent claim 348 recites five steps in this process. The first step (A) provides for one or more chemically modified nucleotides and an oligo- or polynucleotide. The former are capable of incorporating into an oligo- or polynucleotide, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from nucleotides, oligonucleotides and polynucleotides, the latter also being capable of incorporating into an oligo- or polynucleotide. The chemical modification renders the chemically

modified nucleotides (i) self-signaling or self-indicating or self-detecting; or (ii) comprising a label capable of providing directly or indirectly a detectable signal.

In the second step (B), the elements recited in the providing step (A) are incorporated into the oligo- or polynucleotide, thereby preparing a labeled oligo- or polynucleotide of interest. That labeled oligo- or polynucleotide comprises one or more chemically modified nucleotides selected from the group consisting of base-modified, sugar modified and phosphate modified nucleotides. The base modified nucleotides include non-disruptively labeled nucleotides and disruptively labeled nucleotides. The present Examiner may recall that when first filed, Applicants' specification included the complete disclosure of Ward *et al.*, Serial No. 06/225,223, filed on April 17, 1981. Ward's disclosure, directed to non-disruptive base modifications, covered the first fifty-two (52) pages of the specification. As effected by Applicants' September 28, 1995 Preliminary Amendment, three patents have now been issued in the Ward family, including U.S. Patents Nos. 4,711,955; 5,328,824; and 5,449,767. Since Applicants' Preliminary Amendment, a fourth patent, U.S. Patent No. 5,476,928 was issued on December 19, 1995. The issuance of this fourth patent has also been indicated by the above amendment to page 2. A copy of U.S. Patent No. 5,476,928 is attached to this Supplemental Amendment as Exhibit 1. Two U.S. patents have also been issued in the family to which the present application belongs; these include U.S. Patent Nos. 5,241,060 and 5,260,433, issued on August 31, 1993 and November 9, 1993, respectively.

The first fifty-two pages corresponding to Ward's disclosure were deleted by amendment in the predecessor application and the information in Ward's disclosure was fully incorporated by reference into Applicants' present specification. Therefore, chemically modified nucleotides, such as Ward's, in which the base moiety is non-disruptively modified with a moiety that represents at least one component of a signaling moiety, are directly supported by Applicants' disclosure, which also supports chemically modified nucleotides that are modified disruptively and semi-disruptively in the non-Ward positions. Thus, the chemically modified nucleotides set forth in independent claim 348 include nucleotides in which the base is modified non-disruptively, disruptively and semi-disruptively (nucleotide (i)), and nucleotides in which the sugar moiety or the phosphate moiety are modified (nucleotides (ii) and (iii)), those positions representing disruptive and semi-disruptive modifications.

The last three steps in the sequencing process of claim 348 include transferring the labeled oligo- or polynucleotide of interest to a sequencing gel (step (C)), separating the labeled oligo- or polynucleotide of interest from other nucleic acids not of interest (step (D)), and detecting directly or indirectly the presence of the labeled oligo- or polynucleotide (step (E)).

Other embodiments are described in the claims that depend from claim 348. These include the nature of the linkage group (claims 349-358); enzymatic incorporation (claims 359-361); the use of nucleoside di- or tri-phosphates (claim 362); template dependent or template independent incorporation (claims 363-364); incorporation of internal or external modified nucleotides (claims 365-367); electrophoretic separation (claim 368); and direct detection including the use of fluoresceinated nucleotides (claims 369-372).

It is believed that no new matter has been entered by the addition of new claims 337-372, each of which constitutes subject matter to which Applicants are fully and duly entitled to claim as part of their broad and complete disclosure.

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**SUMMARY AND CONCLUSIONS**

Claims 284-372, including newly added claims 337-372, are being presented for further examination on the merits in this application. No new matter is believed to have been entered by the presentation of the new claims.

The fee for new claims 337-372 is \$498.00, based upon the presentation of thirty-eight (38) new claims ( $38 \times \$22.00$  for large entity = \$418.00) and one (1) new independent claim ( $1 \times \$80.00 = \$80.00$ ) above the pending and previously paid fifty-five (55) total claims and three (3) independent claims. The Patent and Trademark Office is hereby authorized to charge the amount of \$498.00 for new claims 337-372 to Deposit Account No. 05-1135. If any other fee is due in connection with this Supplemental Amendment, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135, or to credit overpayment thereto.

If it would be helpful to expediting prosecution of this application, the undersigned may be contacted during normal business hours at (212) 583-0100.

An early indication of the allowable condition of the pending claims is respectfully requested.

Respectfully submitted,



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